

**REMARKS**

Claim 22 has been amended. Claim 25 has been added. Claims 22-25 are currently pending in this application.

Support for the amendments to Claim 22 can be found in original Claim 1 and throughout the specification, for example, on page 39, third paragraph, and page 41, second paragraph.

Support for the subject matter of new Claim 25 can be found, for example, on page 8, paragraph 4.

Thus, Applicants respectfully submit that this amendment is fully supported by the specification as originally filed and that no question of new matter arises. Entry of this Amendment is, therefore, respectfully requested.

**Interpretation of the term “prussic acid”**

Solely to facilitate prosecution and without acquiescence, Applicants have amended the claims to recite “hydrogen cyanide” which the specification clearly sets forth as an alternative to prussic acid (see page 39, third paragraph and page 41, second paragraph).

**Rejections Under 35 U.S.C. § 103(a)**

The Examiner rejects Claims 22-24 under 35 U.S.C. § 103(a) as obvious over Kirchner et al. (U.S. Patent No. 6,337,196) or by the Patent Cooperation Treaty counterpart application to Kirchner (WO 98/30711) (Final Action at page 2).

Applicants respectfully traverse.

The Examiner alleges that Kirchner et al. disclose an enzymatic method of synthesizing optically active cyanohydrins from hydrogen cyanide and a carbonyl compound using hydroxynitrile lyase immobilized on cellulose with a water content 40% in a single phase of

ethyl acetate saturated with an aqueous buffer (Final Action at page 2, paragraph 5). The Examiner acknowledges that the references fail to disclose "saturating the immiscible solvent after the addition of prussic acid," as claimed by the Applicants (Final Action at page 3, paragraph 2). However, since the Examiner considers prussic acid to be a saturated aqueous solution of HCN, the Examiner concludes that the final water content of the reaction mixture claimed by the Applicants would be the same whether the reaction mixture was saturated with water before or after the addition of prussic acid (Final Action, page 3, paragraphs 3-6).

Solely to facilitate prosecution and without acquiescing to the rejection, Applicants have amended Claim 22 to recite a method for producing an optically active cyanohydrin comprising adding hydrogen cyanide and either water or an aqueous buffer to an organic solvent that is substantially immiscible with water. Hydrogen cyanide is anhydrous HCN, which, as indicated in the specification, can be provided in liquid or gaseous form (page 39, paragraph 3). Thus, in the reaction scheme recited in Applicants' Claim 22, the reaction mixture comprising an organic solvent is saturated with water or aqueous buffer in the presence of hydrogen cyanide.

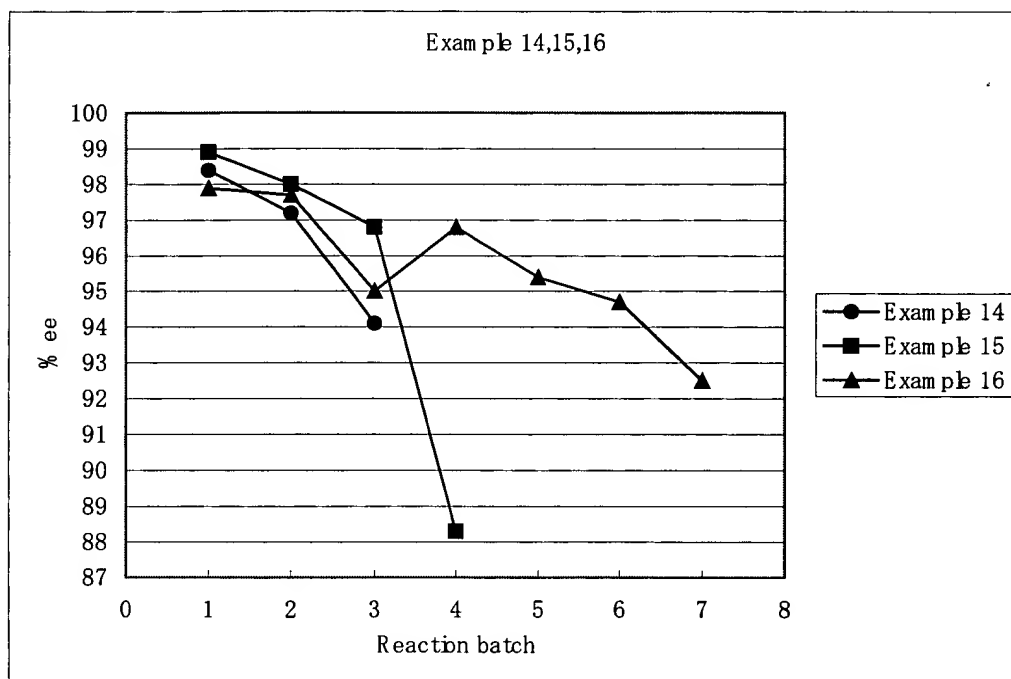
In contrast, in the reaction scheme disclosed by Kirchner et al., the organic solvent is saturated with water before HCN is added to the organic solvent. In Kirchner et al.'s reaction scheme, excess water is first added to an organic solvent (see, for example, Examples 13-16). The aqueous phase is then removed to produce a water-saturated organic solvent. Kirchner et al. then add hydrogen cyanide to the water-saturated organic solvent. The water content of the reaction mixture disclosed by Kirchner et al. is the same before and after the addition of HCN. For example, in Example 15 of Kirchner et al., 1.34 % by weight of water is added to the t-butyl methyl ether reaction solvent to saturation. Hydrogen cyanide (prussic acid, hydrocyanic acid) is then added to the t-butyl methyl ether saturated with 1.34 % by weight water. Hydrogen cyanide

increases the solubility of water in an organic solvent. Therefore, when hydrogen cyanide is added to the reaction solution of t-butyl methyl ether and 1.34 % by weight water, the reaction solution is no longer saturated with water. For example, one skilled in the art would recognize that when 1.5 M hydrogen cyanide is dissolved in t-butyl methyl ether, the amount of water to saturate the reaction solution increases to 4 % by weight. Thus, the reaction mixture is no longer saturated. In contrast, Applicants' method ensures that the reaction mixture solvent is saturated with water. An organic solvent saturated with water in the presence of hydrogen cyanide has a higher water content than the same organic solvent saturated with water in the absence of hydrogen cyanide. Kirchner et al. cannot provide any motivation for saturating the reaction mixture in the presence of hydrogen cyanide because they did not recognize the benefit of the increased water content.

The water content of the reaction mixture for the immobilized lyase reaction to produce optically active cyanohydrin can impact the aldehyde conversion ratio, and the optical purity (% ee) of the cyanohydrin product. As exemplified in Table 1 and Figure 1 of Applicants' specification, maintaining a high water content of the immobilized enzyme, and a commensurately high water content of the reaction system as reflected in the ratio of the volume of water present in the reaction system to the volume of the organic phase, provides a high aldehyde conversion ratio. The production of cyanohydrin in a reaction system includes both enzymatic and non-enzymatic reaction pathways. The enzymatic reaction pathway is highly stereo-specific whereas the non-enzymatic reaction pathway is not stereo-selective. The enzymatic reaction pathway requires that the immobilized enzyme be substantially surrounded by water (page 11, paragraphs 4-5). Therefore, when the immobilized lyase phase is not sufficiently hydrated, the conversion efficiency and optical purity of the cyanohydrin product

will decrease. A decrease in the optical purity (% ee) of the cyanohydrin product indicates that the enzymatic reaction pathway is deactivated.

Indeed, the actual experiments in Kirchner et al., demonstrate that the immobilized lyase is deactivated upon repeated use of the immobilized lyase and results in a decrease in the optical purity of the cyanohydrin. A summary of the relationship between the number of reaction batches and the optical purity of the cyanohydrin produced in Examples 14-16 of Kirchner et al. are provided in the following figure:



In contrast, Example 9 and Figure 4 of Applicants' specification, for example, demonstrate that when using a high water content reaction mixture prepared by saturating the organic solvent in the presence of HCN, the optical purity (% ee) does not decrease even when the water-saturated solvent phase having a high water content is used more than 20 times.

Thus, Kirchner et al. do not teach or suggest each of the elements recited in Applicants' Claim 22, and furthermore, by not recognizing the impact of water content in the reaction mixture, fail to provide a motivation to use an increased water content in the reaction mixture by saturating the organic solvent that is substantially immiscible with water or an aqueous buffer after hydrogen cyanide is added. Moreover, having provided no motivation, Kirchner et al. cannot provide any expectation of success. "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference . . . must teach or suggest all claim limitations." (*MPEP* § 2143 at 2100-124 (2003)).

For at least these reasons, Applicants' independent Claim 22 is non-obvious under 35 U.S.C. § 103(a) over Kirchner et al.

Since independent Claim 22 is herein shown to be non-obvious over Kirchner et al., dependent claims which depend from independent Claim 22 are herein shown to be non-obvious over Kirchner et al. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is also non-obvious.).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 22-24 under 35 U.S.C. § 103(a) over Kirchner et al.

### **CONCLUSION**

In view of the foregoing Amendments and Remarks, Applicants respectfully submit that the cited references cannot render the claimed invention obvious. Applicants therefore request

the Examiner's reconsideration of the application and the timely allowance of pending Claims  
22-25.

If this response does not put the claims in condition for allowance, Applicants earnestly  
request the Examiner to contact their representative at 650.849.6661.

If there is any additional fee due in connection with the filing of their Amendment, please  
charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

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